JS 44 (Rev. 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Lupin Atlantis Holding S.A.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)

John J. Higson, Dilworth Paxson LLP, 1500 Market St. Ste. 3500E, Philadelphia, PA 19102 215-575-7000

DEFENDANTS

APOTEX INC., APOTEX CORP., and ETHYPHARM S.A.,

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus - Alien Detainee
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 U.S.C. § 271(e)(2)

Brief description of cause:
Patent infringement action (ANDA) re Pharmaceutical product under name "Antara"

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☑ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Gene E.K. Pratter DOCKET NUMBER 10-cv-03897

DATE 3/18/11

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA — DESIGNATION FORM to be used by counsel to indicate the category of the case for the purpose of assignment to appropriate calendar.

Address of Plaintiff: Bachstrasse 56, 8200 Schaffhausen SH, Switzerland

Address of Defendant: 150 Signet Drive, North York, Toronto, Ontario, Canada, M9L 1T9

Place of Accident, Incident or Transaction: _____
(Use Reverse Side For Additional Space)

Does this civil action involve a nongovernmental corporate party with any parent corporation and any publicly held corporation owning 10% or more of its stock?
(Attach two copies of the Disclosure Statement Form in accordance with Fed.R.Civ.P. 7.1(a)) Yes ☑ No ☐

Does this case involve multidistrict litigation possibilities? Yes ☑ No ☐

RELATED CASE, IF ANY:
Case Number: 10-cv-03897 Judge Gene E.K. Pratter Date Terminated: _____

Civil cases are deemed related when yes is answered to any of the following questions:

1. Is this case related to property included in an earlier numbered suit pending or within one year previously terminated action in this court? Yes ☐ No ☑
2. Does this case involve the same issue of fact or grow out of the same transaction as a prior suit pending or within one year previously terminated action in this court? Yes ☐ No ☑
3. Does this case involve the validity or infringement of a patent already in suit or any earlier numbered case pending or within one year previously terminated action in this court? Yes ☑ No ☐
4. Is this case a second or successive habeas corpus, social security appeal, or pro se civil rights case filed by the same individual? Yes ☐ No ☑

CIVIL: (Place ✔ in ONE CATEGORY ONLY)

A. *Federal Question Cases:*
1. ☐ Indemnity Contract, Marine Contract, and All Other Contracts
2. ☐ FELA
3. ☐ Jones Act-Personal Injury
4. ☐ Antitrust
5. ☑ Patent
6. ☐ Labor-Management Relations
7. ☐ Civil Rights
8. ☐ Habeas Corpus
9. ☐ Securities Act(s) Cases
10. ☐ Social Security Review Cases
11. ☐ All other Federal Question Cases
(Please specify)

B. *Diversity Jurisdiction Cases:*
1. ☐ Insurance Contract and Other Contracts
2. ☐ Airplane Personal Injury
3. ☐ Assault, Defamation
4. ☐ Marine Personal Injury
5. ☐ Motor Vehicle Personal Injury
6. ☐ Other Personal Injury (Please specify)
7. ☐ Products Liability
8. ☐ Products Liability — Asbestos
9. ☐ All other Diversity Cases
(Please specify)

ARBITRATION CERTIFICATION
(Check Appropriate Category)

I, John J. Higson, counsel of record do hereby certify:

☐ Pursuant to Local Civil Rule 53.2, Section 3(c)(2), that to the best of my knowledge and belief, the damages recoverable in this civil action case exceed the sum of $150,000.00 exclusive of interest and costs;

☑ Relief other than monetary damages is sought.

DATE: 3/18/2011 _____ Attorney-at-Law 80720 Attorney I.D.#

NOTE: A trial de novo will be a trial by jury only if there has been compliance with F.R.C.P. 38.

I certify that, to my knowledge, the within case is not related to any case now pending or within one year previously terminated action in this court except as noted above.

DATE: n/a see above _____ Attorney-at-Law _____ Attorney I.D.#

CIV. 609 (6/08)

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA — DESIGNATION FORM to be used by counsel to indicate the category of the case for the purpose of assignment to appropriate calendar.

Address of Plaintiff: Bachstrasse 56, 8200 Schaffhausen SH, Switzerland

Address of Defendant: 150 Signet Drive, North York, Toronto, Ontario, Canada, M9L 1T9

Place of Accident, Incident or Transaction: _____

(*Use Reverse Side For Additional Space*)

Does this civil action involve a nongovernmental corporate party with any parent corporation and any publicly held corporation owning 10% or more of its stock?

(Attach two copies of the Disclosure Statement Form in accordance with Fed.R.Civ.P. 7.1(a)) Yes ☑ No ☐

Does this case involve multidistrict litigation possibilities? Yes ☑ No ☐

RELATED CASE, IF ANY:

Case Number: 10-cv-03897 Judge Gene E.K. Pratter Date Terminated: _____

Civil cases are deemed related when yes is answered to any of the following questions:

1. Is this case related to property included in an earlier numbered suit pending or within one year previously terminated action in this court? Yes ☐ No ☑
2. Does this case involve the same issue of fact or grow out of the same transaction as a prior suit pending or within one year previously terminated action in this court? Yes ☐ No ☑
3. Does this case involve the validity or infringement of a patent already in suit or any earlier numbered case pending or within one year previously terminated action in this court? Yes ☑ No ☐
4. Is this case a second or successive habeas corpus, social security appeal, or pro se civil rights case filed by the same individual? Yes ☐ No ☑

CIVIL: (Place ✔ in ONE CATEGORY ONLY)

A. *Federal Question Cases*:

1. ☐ Indemnity Contract, Marine Contract, and All Other Contracts
2. ☐ FELA
3. ☐ Jones Act-Personal Injury
4. ☐ Antitrust
5. ☑ Patent
6. ☐ Labor-Management Relations
7. ☐ Civil Rights
8. ☐ Habeas Corpus
9. ☐ Securities Act(s) Cases
10. ☐ Social Security Review Cases
11. ☐ All other Federal Question Cases (Please specify)

B. *Diversity Jurisdiction Cases*:

1. ☐ Insurance Contract and Other Contracts
2. ☐ Airplane Personal Injury
3. ☐ Assault, Defamation
4. ☐ Marine Personal Injury
5. ☐ Motor Vehicle Personal Injury
6. ☐ Other Personal Injury (Please specify)
7. ☐ Products Liability
8. ☐ Products Liability — Asbestos
9. ☐ All other Diversity Cases (Please specify)

ARBITRATION CERTIFICATION

(*Check Appropriate Category*)

I, John J. Higson, counsel of record do hereby certify:

☐ Pursuant to Local Civil Rule 53.2, Section 3(c)(2), that to the best of my knowledge and belief, the damages recoverable in this civil action case exceed the sum of $150,000.00 exclusive of interest and costs;

☑ Relief other than monetary damages is sought.

DATE: 3/18/2011 _____ Attorney-at-Law 80720 Attorney I.D.#

NOTE: A trial de novo will be a trial by jury only if there has been compliance with F.R.C.P. 38.

I certify that, to my knowledge, the within case is not related to any case now pending or within one year previously terminated action in this court except as noted above.

DATE: n/a see above _____ Attorney-at-Law _____ Attorney I.D.#

CIV. 609 (6/08)

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

CASE MANAGEMENT TRACK DESIGNATION FORM

Lupin Atlantis Holdings S.A.,	:	CIVIL ACTION
v.	:	
APOTEX INC., APOTEX CORP., and ETHYPHARM S.A.,	:	NO.

In accordance with the Civil Justice Expense and Delay Reduction Plan of this court, counsel for plaintiff shall complete a Case Management Track Designation Form in all civil cases at the time of filing the complaint and serve a copy on all defendants. (See § 1:03 of the plan set forth on the reverse side of this form.) In the event that a defendant does not agree with the plaintiff regarding said designation, that defendant shall, with its first appearance, submit to the clerk of court and serve on the plaintiff and all other parties, a Case Management Track Designation Form specifying the track to which that defendant believes the case should be assigned.

SELECT ONE OF THE FOLLOWING CASE MANAGEMENT TRACKS:

(a) Habeas Corpus – Cases brought under 28 U.S.C. § 2241 through § 2255. ☐

(b) Social Security – Cases requesting review of a decision of the Secretary of Health and Human Services denying plaintiff Social Security Benefits. ☐

(c) Arbitration – Cases required to be designated for arbitration under Local Civil Rule 53.2. ☐

(d) Asbestos – Cases involving claims for personal injury or property damage from exposure to asbestos. ☐

(e) Special Management – Cases that do not fall into tracks (a) through (d) that are commonly referred to as complex and that need special or intense management by the court. (See reverse side of this form for a detailed explanation of special management cases.) ☑

(f) Standard Management – Cases that do not fall into any one of the other tracks. ☐

3-18-2011		Lupin Atlantis Holdings, S.A.
Date	**Attorney-at-law**	**Attorney for**
215-575-7000	215-575-7200	jhigson@dilworthlaw.com
Telephone	**FAX Number**	**E-Mail Address**

(Civ. 660) 10/02

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

LUPIN ATLANTIS HOLDINGS S.A.,

Plaintiff,

v.

APOTEX INC., APOTEX CORP., and ETHYPHARM S.A.,

Defendants.

COMPLAINT

Plaintiff Lupin Atlantis Holdings S.A., by its attorneys, for its complaint against Apotex Inc., Apotex Corp. (collectively, "Apotex") and Ethypharm S.A., allege as follows:

THE PARTIES

1. Plaintiff Lupin Atlantis Holdings S.A. ("Lupin Atlantis") is a corporation organized and existing under the laws of Switzerland, with a principal place of business at Bachstrasse 56, 8200 Schaffhausen SH, Switzerland.

2. Upon information and belief, Defendant Apotex Inc. is a company organized and existing under the laws of Canada with a principal place of business at 150 Signet Drive, North York, Toronto, Ontario, Canada, M9L 1T9. Apotex Inc. is owned by Apotex Pharmaceutical Holdings Inc., which also owns Apotex Corp.

3. Upon information and belief, Apotex Inc. is, alone and/or through Apotex Corp., in the business of, among other activities, manufacturing and selling copies of

branded pharmaceutical products which are used and sold throughout the United States, including in this judicial district.

4. Upon information and belief, Defendant Apotex Corp. is a corporation organized and existing under the laws of Delaware, and is a owned by Apotex Pharmaceutical Holdings Inc., which also owns Apotex Inc. Apotex Corp. has a principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida, 33326.

5. Upon information and belief, Apotex Corp. is in the business of, among other activities, offering for sale, selling and/or importing copies of branded pharmaceutical products manufactured by, among others, Apotex Inc., throughout the United States, including in this judicial district.

6. Upon information and belief, Defendant Ethypharm S.A. ("Ethypharm") is a corporation organized and existing under the laws of France, with its principal offices at 194 Bureaux de la Colline, 922 13 St. Cloud, France.

7. Upon information and belief, Apotex Inc. and Apotex Corp. collaborated in the research and development of Apotex's Abbreviated New Drug Application ("ANDA") No. 202252 for capsules that contain 43 mg and 130 mg of fenofibrate as the active ingredient ("the Apotex ANDA Product"), continue to collaborate in seeking approval of that application by the FDA, and intend to collaborate in the commercial manufacture, marketing, offer for sale and sale of the Apotex ANDA Product throughout the United States, including in this judicial district, in the event the FDA approves the Apotex ANDA.

JURISDICTION AND VENUE

8. This is a civil action arising under the patent laws of the United States, Title 35, United States Code, for infringement of U.S. Patent 7,101,574 ("the '574 patent") and U.S. Patent No. 7,863,331 ("the '331 patent"). This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

9. Upon information and belief, Apotex Inc. is subject to personal jurisdiction in this judicial district because it has purposely availed itself of the benefits

and protections of this Commonwealth's laws such that it should reasonably anticipate being haled into court in this judicial district. On information and belief, Apotex Inc., alone and/or through Apotex Corp., markets and sells generic drugs throughout the United States, and in particular within this judicial district, and therefore Apotex Inc. has engaged in systematic and continuous business within this judicial district.

10. Upon information and belief, Apotex Corp. is subject to personal jurisdiction in this judicial district because, *inter alia*, Apotex Corp., alone and/or with Apotex Inc., has purposely availed itself of the benefits and protections of this Commonwealth's laws such that it should reasonably anticipate being haled into court in this judicial district. Upon information and belief, Apotex Corp., alone and/or with Apotex Inc., markets and sells generic drugs throughout the United States, and in particular within this judicial district, and therefore Apotex Corp. has engaged in systematic and continuous business within this judicial district.

11. Upon information and belief, Apotex Corp. and Apotex Inc. market Apotex's generic drug products to persons residing within this judicial district, for example, via their website.

12. Upon information and belief, Apotex Corp. and Apotex Inc. offer Apotex's generic drug products for sale to persons residing within this judicial district on third-party websites that these persons can use to purchase Apotex products for shipment to and within this judicial district.

13. Upon information and belief, persons residing within this judicial district purchase generic drug products, including Apotex products, from Apotex Inc. (itself or through Apotex Corp.) in this judicial district.

14. Upon information and belief, persons residing within this judicial district purchase generic drug products, including Apotex products, from Apotex Corp. in this judicial district.

15. Upon information and belief, Apotex Inc. (itself or through Apotex Corp.) receives revenue from the sales and marketing of generic drug products, including Apotex products, within this judicial district.

16. Upon information and belief, Apotex Corp. receives revenue from the sales and marketing of generic drug products, including Apotex products, within this judicial district.

17. Upon information and belief, Apotex Inc., alone and/or through Apotex Corp., intends to market and sell the Apotex ANDA Product, if approved, to residents of this judicial district.

18. Upon information and belief, Apotex Inc. has availed itself of the benefits of this court. In Civil Action No. 2:06-cv-02768-MSG (E.D. Pa.), Apotex Inc. brought an action against Cephalon Inc., Barr Laboratories, Inc., Mylan Laboratories, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Ranbaxy Laboratories, Ltd., and Ranbaxy Pharmaceuticals, Inc. alleging unfair competition involving the drug product Provigil® and also requesting declaratory judgment of non-infringement, invalidity, and unenforceability of patents on such product. In a related action, Civil Action No. 2:09-cv-02416-MSG (E.D. Pa.), Apotex Inc. brought a declaratory judgment suit against Cephalon Inc. under, *inter alia*, the Patent Laws of the United States (35 U.S.C. § 1 et seq.), and the Hatch-Waxman Act (21 U.S.C. § 301 et seq.). In both actions, Apotex Inc. admitted that venue in this judicial district was proper.

19. Upon information and belief, Apotex Inc. and Apotex Corp. admitted in Civil Action No. 2:01-cv-02169-MMB (E.D. Pa.), an action brought against both companies arising under, *inter alia*, the Patent Laws of the United States (35 U.S.C. § 1 et seq.), and the Hatch-Waxman Act (21 U.S.C. § 301 et seq., that venue in this judicial district was proper. In another case pending in this district, upon information and belief, Apotex Inc. and Apotex Corp. also submitted a Rule 12(b)(6) motion in Civil Action No. 2:05-cv-05500-MMB (E.D. Pa.), without objecting to personal jurisdiction or venue.

20. Upon information and belief, Ethypharm is in the business of, among other activities, manufacturing pharmaceutical products for importation into and sale throughout the United States and promotes the importation and sale of such products, including in this judicial district.

21. Apotex Inc., Apotex Corp., and Ethypharm are subject to personal jurisdiction in this judicial district.

22. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

BACKGROUND

23. Lupin Atlantis is the owner of the approved New Drug Application ("NDA") No. 21-695 for ANTARA® capsules.

24. On information and belief, Apotex Corp. submitted ANDA No. 202252 to the FDA under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of generic copies of ANTARA® capsules.

25. The ANTARA® capsules contain 43 mg and 130 mg of micronized fenofibrate as the active ingredient, and are currently approved for the treatment of hypercholesterolemia and hypertriglyceridemia.

26. Upon information and belief, the Apotex ANDA Product that is the subject of Apotex's ANDA No. 202252 are capsules containing 43 mg and 130 mg of fenofibrate as the active ingredient.

THE PATENTS-IN-SUIT

27. On September 5, 2006, the U.S. Patent and Trademark Office ("USPTO") duly and legally issued the '574 patent titled "Pharmaceutical Composition Containing Fenofibrate and the Preparation Method." A true and correct copy of the '574 patent is attached hereto as Exhibit A.

28. On January 4, 2011, the USPTO duly and legally issued U.S. Patent No. 7,863,331 (the "'331 patent"), titled "Pharmaceutical Composition Containing Fenofibrate and Method for the Preparation Thereof." A true and correct copy of the '331 patent is attached hereto as Exhibit B.

29. Ethypharm is the owner of the '574 patent, which discloses and claims, inter alia, a pharmaceutical composition containing fenofibrate and a method for preparing the composition.

30. Ethypharm is also the owner of the '331 patent, which discloses and claims, *inter alia*, methods of treatment using compositions containing fenofibrate.

31. Lupin Atlantis holds a license from Ethypharm under the '574 and '331 patents that contains provisions granting Lupin Atlantis the right to enforce the '574 and '331 patents in the case of an ANDA filing by a third party.

32. As owner of the '574 and '331 patents and licensor of the '574 and '331 patents to Lupin Atlantis, Defendant Ethypharm is jointly interested with, and contractually obligated to cooperate with, Lupin Atlantis in this cause of action, including without limitation joining this action if necessary. Although requested to file suit as Co-Plaintiff, Ethypharm has not, as of the date of the filing of this action, agreed to do so. For that reason, Ethypharm is named as a defendant.

COUNT I FOR PATENT INFRINGEMENT

(Infringement of the '574 patent under 35 U.S.C. § 271(e)(2))

33. Lupin Atlantis incorporates paragraphs 1-32 of this Complaint as if fully set forth herein.

34. Upon information and belief, Apotex sent a letter dated February 17, 2011, to Lupin Atlantis, Ethypharm, Lupin (Europe) Ltd, and Lupin Pharmaceuticals, Inc. which purported to comply with the provisions of 21 U.S.C. § 355(j)(2)(B). This letter purportedly advised Lupin Atlantis and Ethypharm that Apotex's ANDA contains a Paragraph IV certification with respect to the '574 patent, and that no valid, enforceable claim of the '574 patent would be infringed by the manufacture, importation, use, sale or offer for sale of the Apotex ANDA Product.

35. Upon information and belief, the '574 patent was listed in the FDA publication entitled Approved Drug Products and Therapeutic Equivalence Evaluations ("the Orange Book") relative to ANTARA®.

36. Upon information and belief, Apotex Corp. submitted Apotex ANDA No. 202252 to the FDA for purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of a generic copy of the ANTARA® product prior to the expiration of the '574 patent.

37. Upon information and belief, the Apotex ANDA contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") asserting that, in

its opinion, the '574 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of the Apotex ANDA Product.

38. 21 U.S.C. § 355(j)(2)(A)(vii)(IV) requires, inter alia, certification by the ANDA applicant that the subject patent, here the '574 patent, is "invalid or will not be infringed by the manufacture, use, offer for sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, inter alia, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

39. Upon information and belief, at the time Apotex Corp.'s letter of February 17, 2011, was mailed (this letter purportedly serving as a notice of Paragraph IV certification relative to the '574 patent, i.e., "Apotex's Notice of Certification"), Apotex Corp. and/or Apotex Inc. were aware of the statutory provisions and regulations referred to in paragraph 38, supra.

40. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding all bases for noninfringement of the '574 patent but does not do so. Instead, Apotex offers only conclusory statements.

41. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding all bases for invalidity of the '574 patent, but does not allege invalidity of any claims of the '574 patent. Instead, Apotex states in its Notice of Certification that it "*reserves the right to demonstrate additional factual and legal bases* concerning noninfringement, *invalidity*, or unenforceability should future information so warrant" (emphasis added).

42. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding alleged unenforceability of the patents-in-suit, but does not allege unenforceability or allege inequitable conduct of the '574 patent. Instead, Apotex states in its Notice of Certification that it "*reserves the right to demonstrate additional factual and legal bases* concerning noninfringement, invalidity, or *unenforceability* should future information so warrant" (emphasis added).

43. Apotex's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

44. By filing ANDA No. 202252 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of the Apotex ANDA Product prior to the expiration of the '574 patent, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, on information and belief, Apotex plans to commercially use, offer for sale, and/or sell the Apotex ANDA Product, and/or to induce or contribute to such activity, and by such actions Apotex would infringe one or more claims of the '574 patent under 35 U.S.C. § 271(a), (b) and/or (c).

45. Upon information and belief, Apotex Corp. and Apotex Inc. participated in, contributed to, aided, and/or induced the submission of Apotex ANDA No. 202252 and its Paragraph IV certification to the FDA. Additionally, upon information and belief, Apotex Corp. and Apotex Inc. will market and/or distribute the Apotex ANDA Product in the United States, and within this judicial district, if Apotex ANDA No. 202252 is approved by the FDA. Apotex Corp. and Apotex Inc. thus are jointly and severally liable for infringement of the '574 patent.

46. This action is being filed within 45 days of receipt by Lupin Atlantis and Ethypharm of the Apotex letter dated February 17, 2011, which purportedly advised Lupin Atlantis and Ethypharm of Apotex's Paragraph IV certification with respect to the '574 patent.

47. Upon information and belief, Apotex had actual and constructive notice of the '574 patent prior to filing Apotex ANDA No. 202252, and Apotex's infringement of the '574 patent has been, and continues to be, willful.

48. Lupin Atlantis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Apotex ANDA No. 202252 be a date that is not earlier than the expiration of the '574 patent, or any later expiration of exclusivity for the '574 patent to which they become entitled.

49. Lupin Atlantis will be irreparably harmed if Apotex is not enjoined from infringing or actively inducing or contributing to infringement of the '574 patent, as Lupin Atlantis has no adequate remedy at law.

COUNT II FOR PATENT INFRINGEMENT

(Infringement of the '331 patent under 35 U.S.C. § 271(e)(2))

50. Lupin Atlantis incorporates paragraphs 1-49 of this Complaint as if fully set forth herein.

51. Upon information and belief, Apotex sent a letter dated February 17, 2011, to Lupin Atlantis, Ethypharm, Lupin (Europe) Ltd, and Lupin Pharmaceuticals, Inc. which purported to comply with the provisions of 21 U.S.C. § 355(j)(2)(B). This letter purportedly advised Lupin Atlantis and Ethypharm that Apotex's ANDA contains a Paragraph IV certification with respect to the '331 patent, and that no valid, enforceable claim of the '331 patent would be infringed by the manufacture, importation, use, sale or offer for sale of the Apotex ANDA Product.

52. Upon information and belief, the '331 patent was listed in the FDA publication entitled Approved Drug Products and Therapeutic Equivalence Evaluations ("the Orange Book") relative to ANTARA®.

53. Upon information and belief, Apotex Corp. submitted Apotex ANDA No. 202252 to the FDA for purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of a generic copy of the ANTARA® product prior to the expiration of the '331 patent.

54. Upon information and belief, the Apotex ANDA contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") asserting that, in its opinion, the '331 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of the Apotex ANDA Product.

55. 21 U.S.C. § 355(j)(2)(A)(vii)(IV) requires, inter alia, certification by the ANDA applicant that the subject patent, here the '331 patent, is "invalid or will not be infringed by the manufacture, use, offer for sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, inter alia, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

56. Upon information and belief, at the time Apotex's letter of February 17, 2011, was mailed (this letter purportedly serving as a notice of Paragraph IV certification relative to the '331 patent, i.e., "Apotex's Notice of Certification"), Apotex was aware of the statutory provisions and regulations referred to in paragraph 55, supra.

57. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding all bases for noninfringement of the '331 patent but does not do so. Instead, Apotex Corp. offers only conclusory statements.

58. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding all bases for invalidity of the '331 patent, but does not allege invalidity of any claims of the '331 patent. Instead, Apotex states in its Notice of Certification that it "*reserves the right to demonstrate additional factual and legal bases* concerning noninfringement, *invalidity*, or unenforceability should future information so warrant" (emphasis added).

59. Apotex's Notice of Certification is required by statute and regulation to provide a full and detailed explanation regarding alleged unenforceability of the patents-in-suit, but does not allege unenforceability or allege inequitable conduct of the '331 patent. Instead, Apotex states in its Notice of Certification that it "*reserves the right to*

demonstrate additional factual and legal bases concerning noninfringement, invalidity, or *unenforceability* should future information so warrant" (emphasis added).

60. Apotex's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

61. By filing ANDA No. 202252 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of the Apotex ANDA Product prior to the expiration of the '331 patent, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, on information and belief, Apotex plans to commercially use, offer for sale, and/or sell the Apotex ANDA Product, and/or to induce or contribute to such activity, and by such actions Apotex would infringe one or more claims of the '331 patent under 35 U.S.C. § 271(a), (b) and/or (c).

62. Upon information and belief, Apotex Corp. and Apotex Inc. participated in, contributed to, aided, and/or induced the submission of Apotex ANDA No. 202252 and its Paragraph IV certification to the FDA. Additionally, upon information and belief, Apotex Corp. and Apotex Inc. will market and/or distribute the Apotex ANDA Product in the United States, and within this judicial district, if Apotex ANDA No. 202252 is approved by the FDA. Apotex Corp. and Apotex Inc. thus are jointly and severally liable for infringement of the '331 patent.

63. This action is being filed within 45 days of receipt by Lupin Atlantis and Ethypharm of the Apotex letter dated February 17, 2011, which purportedly advised Lupin Atlantis and Ethypharm of Apotex's Paragraph IV certification with respect to the '331 patent.

64. Upon information and belief, Apotex had actual and constructive notice of the '331 patent prior to filing Apotex ANDA No. 202252, and Apotex's infringement of the '331 patent has been, and continues to be, willful.

65. Lupin Atlantis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Apotex ANDA No. 202252 be a date that is not earlier than the expiration of the '331 patent, or any later expiration of exclusivity for the '331 patent to which they become entitled.

66. Lupin Atlantis will be irreparably harmed if Apotex is not enjoined from infringing or actively inducing or contributing to infringement of the '331 patent, as Lupin Atlantis has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Lupin Atlantis respectfully requests the following relief:

A. A judgment that Apotex has infringed one or more claims of the '574 patent under 35 U.S.C. § 271(e)(2);

B. A judgment that Apotex has infringed one or more claims of the '331 patent under 35 U.S.C. § 271(e)(2);

C. An order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of Apotex's ANDA No. 202252 be not earlier than the expiration date of the '574 patent or any later expiration of exclusivity for this patent to which it may become entitled;

D. An order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of Apotex's ANDA No. 202252 be not earlier than the expiration date of the '331 patent or any later expiration of exclusivity for this patent to which it may become entitled;

E. A permanent injunction restraining and enjoining Apotex Corp. and Apotex Inc. and each of their officers, agents, servants, employees and those persons acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale or sale within the United States or its territories, or importation into the United States or its territories, of the Apotex ANDA Product, or any product that infringes the '574 patent;

F. A permanent injunction restraining and enjoining Apotex Corp. and Apotex Inc. and each of their officers, agents, servants, employees and those persons acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale or sale within the United States or its territories, or importation into the United States or its territories, of the Apotex ANDA Product, or any product that infringes the '331 patent;

G. Damages and treble damages from Apotex from any commercial activity constituting infringement of the '574 patent;

H. Damages and treble damages from Apotex from any commercial activity constituting infringement of the '331 patent;

I. That Defendant Ethypharm be realigned and named as a Plaintiff in this action;

J. Costs and expenses in this action; and

K. Such other and further relief as this Court determines to be just and proper.

Respectfully submitted,

Date: March 18, 2011

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Exhibit A

(12) **United States Patent**
Criere et al.

(10) **Patent No.: US 7,101,574 B1**
(45) **Date of Patent: Sep. 5, 2006**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD**

(75) Inventors: **Bruno Criere**, Gravigny (FR); **Pascal Suplie**, Montaure (FR); **Philippe Chenevier**, Montréal (CA)

(73) Assignee: **Laboratoires des Produits Ethiques Ethypharm**, Houdan (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 44 days.

(21) Appl. No.: **10/030,262**
(22) PCT Filed: **Jul. 7, 2000**
(86) PCT No.: **PCT/FR00/01971**

§ 371 (c)(1),
(2), (4) Date: **Apr. 17, 2002**

(87) PCT Pub. No.: **WO01/03693**
PCT Pub. Date: **Jan. 18, 2001**

(30) **Foreign Application Priority Data**

Jul. 9, 1999 (FR) 99 08923

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 9/64 (2006.01)
A61K 9/56 (2006.01)
A61K 9/58 (2006.01)

(52) **U.S. Cl.** **424/489**; 424/456; 424/459; 424/462

(58) **Field of Classification Search** 424/489, 424/462, 456, 459, 497, 490; 514/49
See application file for complete search history.

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Primary Examiner—Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm*—Buchanan Ingersoll & Rooney PC

(57) **ABSTRACT**

The invention concerns a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, as solubilizing adjuvant, preferably hydroxypropylmethylcellulose. The cellulose derivative represents less than 20 wt. % of the composition. The association of micronized fenofibrate with a binding cellulose derivative, as solubilizing adjuvant and a surfactant enables enhanced bioavailability of the active principle. The invention also concerns a method for preparing said composition without using any organic solvent.

34 Claims, 4 Drawing Sheets

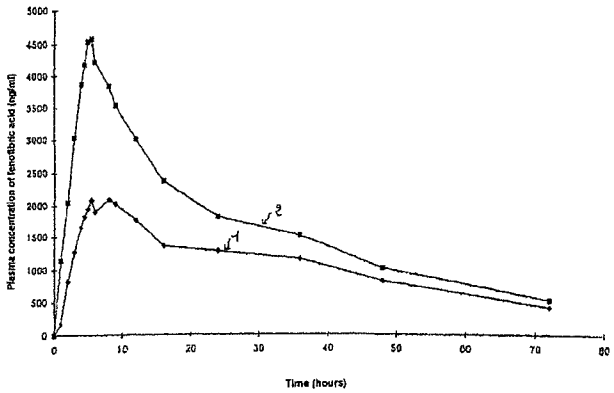

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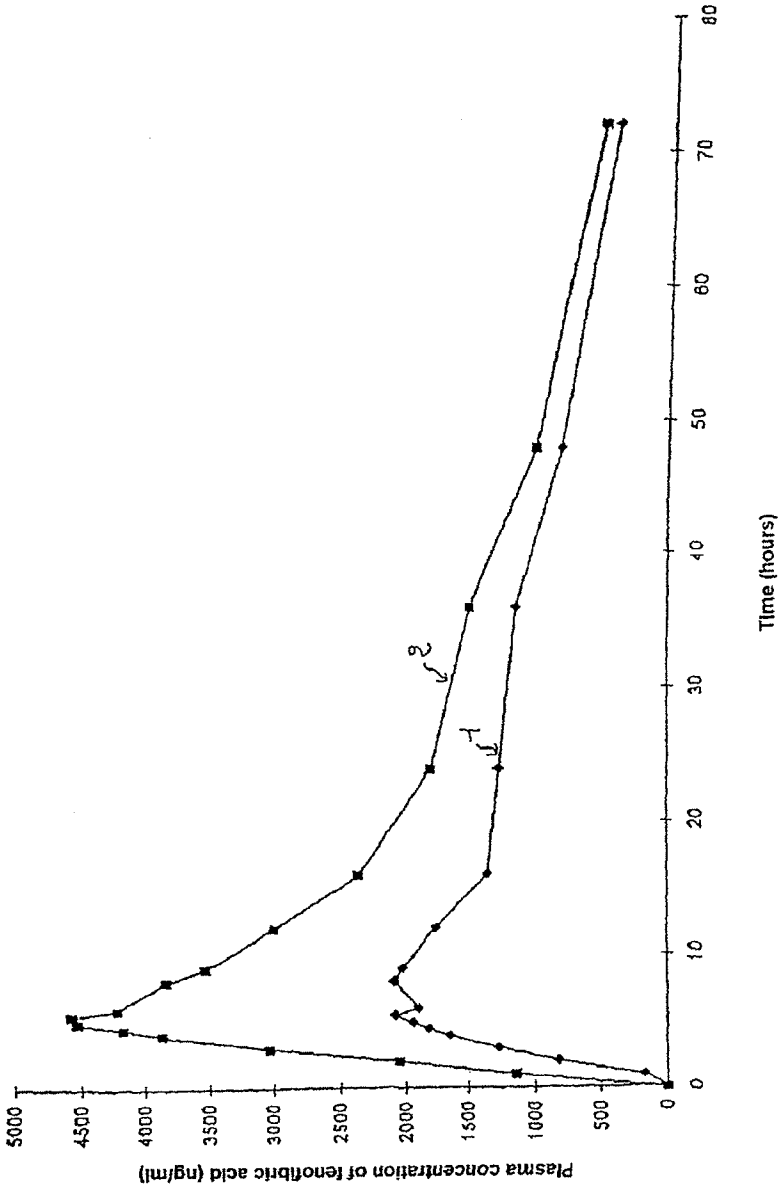
Figure 1


Plasma concentration of fenofibric acid (ng/ml)
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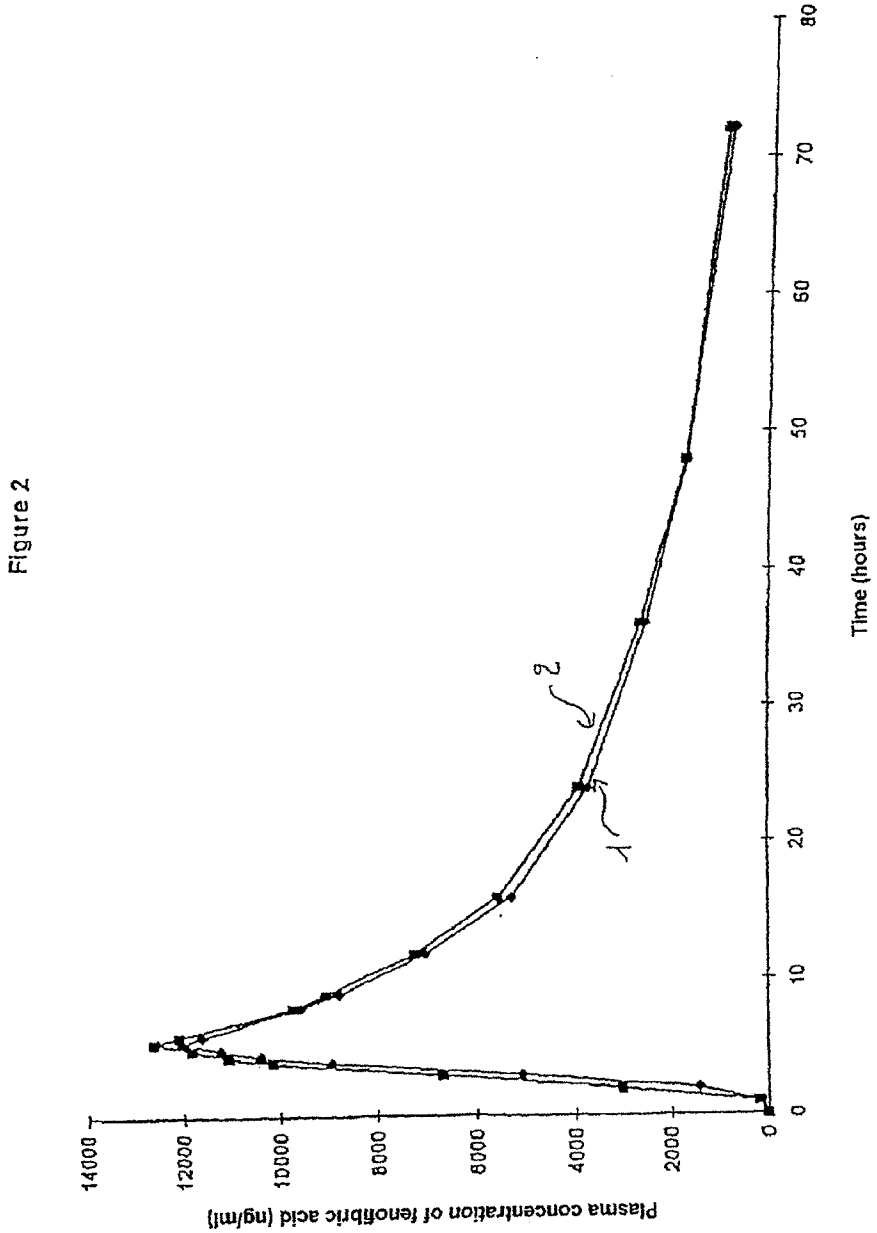
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2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12000
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10
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60
70
80
Time (hours)
2
1

Figure 2

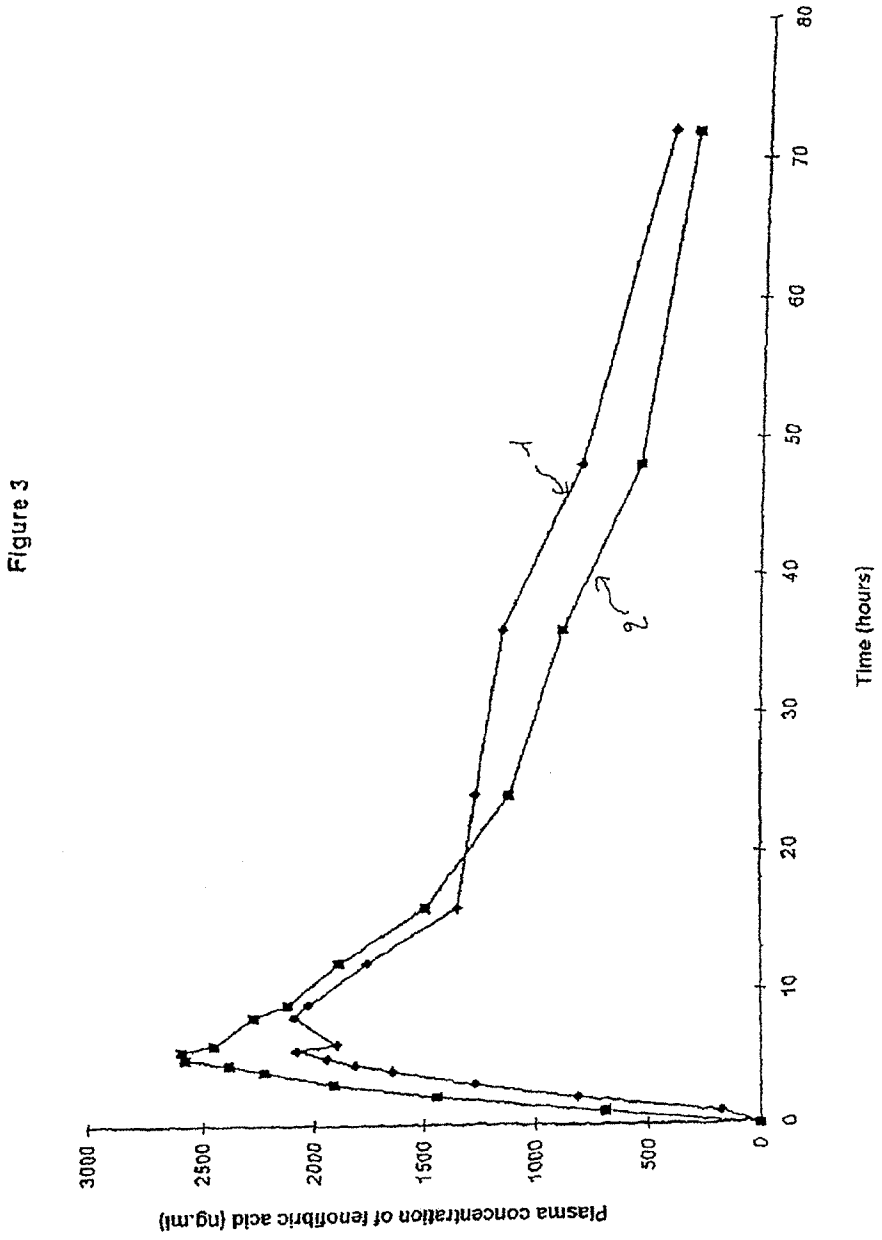
Plasma concentration of fenofibric acid (ng.ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 3

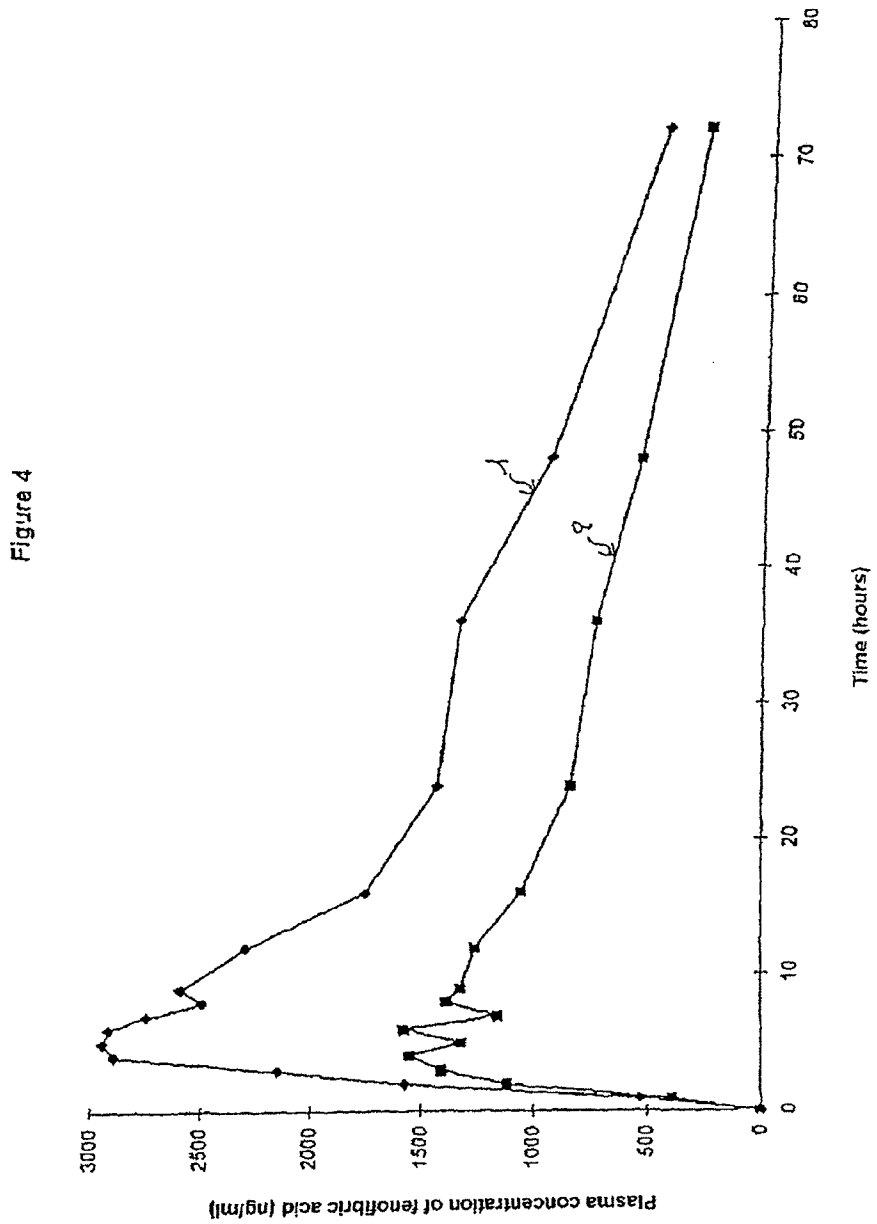
Plasma concentration of fenofibric acid (ng/ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 4

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD

This application is a 371 of PCT/FR00/01971 filed on Jul. 7, 2000.

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited. An increase in its solubility or in its rate of solubilization leads to better digestive absorption.

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline fenofibrate microparticles are less than 50 μm in size. the binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinyl-pyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, which is a solubilization adjuvant, preferably hydroxypropylmethylcellulose (HPMC).

The composition of the invention is advantageously provided as gelatin capsules containing powder or granules, preferably in the form of granules. These granules may in particular be prepared by assembly on neutral microgranules, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension, or by wet granulation of powder, according to which the constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 or Montane® 20, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 μm, preferably 10 μm, even more preferably less than 8 μm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance DIMETHICONE and SIMETHICONE, or lubricants, for instance talc.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably equal to 200 mg.

The present invention also relates to a method for preparing the powder or the granules, the composition of which is described above. This method uses no organic solvent.

According to a first variant, the granules are prepared by assembly on neutral microgranules.

The neutral microgranules have a particle size of between 200 and 1 000 microns, preferably between 400 and 600 microns.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly of neutral microgranules is carried out by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension.

According to a second variant, the granules are obtained by wet granulation of powder. The granulation enables the powders to be made dense and makes it possible to improve their flow properties. It also allows better preservation of the homogeneity, by avoiding the various constituents becoming unmixed.

The micronized fenofibrate, the surfactant, the cellulose derivative and, optionally, the other excipients are mixed, granulated, dried and then calibrated. The wetting solution may be water or an aqueous solution containing the binding cellulose derivative and/or the surfactant.

According to a particular embodiment, the fenofibrate and the other excipients are mixed in a planetary mixer. The wetting solution is added directly to the mixture. The wet mass obtained is granulated with an oscillating granulator, and then dried in an oven. The granules are obtained after passage over an oscillating calibrator.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals.

FIG. **2** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals who have just eaten.

FIG. **3** represents the in vivo release profile of the formulation of example 2B and of a formulation of the prior art in fasting individuals.

FIG. **4** represents the in vivo release profile of the formulation of comparative example 3 and of a formulation of the prior art in individuals who have just eaten.

The invention is illustrated in a nonlimiting way by the following examples.

EXAMPLE 1

Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral microgranules	21
HPMC (Pharmacoat 603 ®)	11.2
Polysorbate ® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9±0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC.

The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral microgranules	20.1
HPMC (Pharmacoat 603 ®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral microgranules is between 400 and 600 μm.

1C) Gelatin Capsules of Microgranules (Y FEN 001)

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral microgranules	17.2
Pharmacoat 603 ® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40° C./75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin Capsule) Conservation time			
0	1 month	3 months	6 months
208.6	192.6	190.8	211.7

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. 1.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	76	119
AUC_{inf} (µg · h/ml)	96	137
C_{max} (µg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the Cmax,

$Elim_{1/2}$: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. 1 by curves 1 and 2, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic Study Carried Out in Individuals Who Have Just Eaten

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. 2.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	244	257
AUC_{inf} (µg · h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. 2 by curves 1 and 2, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals who have just eaten.

EXAMPLE 2

Powder

2A) Granules (X FEN 1992)

Granules having the following composition are prepared

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	71
Lactose	21.5
HPMC (Pharmacoat 603 ®)	5
Sodium lauryl sulfate	2.5

The micronized fenofibrate, the HPMC and the lactose are mixed using a planetary mixer. This mixture is granulated in the presence of a solution of sodium lauryl sulfate.

The flow time of the granules is 7 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (X FEN 1992)	
V0	204 ml
V10	186 ml
V500	168 ml
V1250	164 ml
V10–V500	22 ml

Particle size distribution (X FEN 1992)

Sieve mesh size (mm)	% of oversize mass
0.6	8
0.5	9
0.355	12
0.2	30
0.1	23
0	18

2B) Gelatin Capsules of Granules (Y FEN 002)

Preparation

The micronized fenofibrate is mixed in a PMA mixer (Niro Fielder) with lactose and HPMC, and then wetted with an aqueous solution of sodium lauryl sulfate. The mass obtained is granulated by passage over an oscillating granulator, dried and then calibrated on a sieve with a mesh size of 1.25 mm.

The granules are then packaged in size 1 gelatin capsules at doses of 200 mg of fenofibrate.

Granules of the following composition are obtained.

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	70
Lactose	21.5
Pharmacoat 603 ® (HPMC)	5
Sodium lauryl sulfate	3.5
Content	700 mg/g

Properties of the Granules

The flow time of the granules is 6 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (Y FEN 002)	
V0	216 ml
V10	200 ml
V500	172 ml
V1250	170 ml
V10–V500	28 ml

Particle size distribution (Y FEN 002)

Sieve mesh size (mm)	% of oversize mass
0.6	5
0.5	7

-continued

Particle size distribution (Y FEN 002)

Sieve mesh size (mm)	% of oversize mass
0.355	11
0.2	30
0.1	25
0	22

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results for a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 2B (% dissolved)	82.2	88.5
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 2B dissolves more rapidly than Lipanthyl 200 M.

Stability Tests

The gelatin capsules conserved at 40° C./75% relative humidity are stable for 6 months.

In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	54.2	52.9	49.0
15	81.1	75.8	82.2
25	86.4	79.6	87.2
35	88.8	81.6	89.8
45	90.7	82.9	91.5
55	92.1	83.9	92.7
65	93.2	84.7	93.6

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin capsule)

Conservation time			
0	1 month	3 months	6 months
196.6	190.0	199.8	203.3

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 002 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. 3.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (μg · h/ml)	76	70
AUC_{inf} (μg · h/ml)	96	62
C_{max} (μg/ml)	2.35	2.8
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.033
Elim ½ (hours)	26.7	23.1

The results obtained for Lipanthyl 200 M and for the product of example 2B are represented on FIG. 3 by curves 1 and 2, respectively.

These results show that the composition of example 2B is bioequivalent to that of Lipanthyl 200 M in fasting individuals.

COMPARATIVE EXAMPLE 3

Batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

Theoretical Formula

Products	Theoretical amount (%)
Micronized fenofibrate	75.08
Montanox 80 ®	4.72
Avicel PH 101 ®	5.02
PVP K 30 ®	4.12
Explotab ®	11.06

In Vitro Dissolution Profile

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in the following table.

Time (min)	15	30
Example 3 (% dissolved)	24	40
Lipanthyl 200 N (% dissolved)	47.3	647

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. 4.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 3
AUC_{0-t} (μg · h/ml)	92	47
AUC_{inf} (μg · h/ml)	104	53
C_{max} (μg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 3 are represented on FIG. 4 by curves 1 and 2, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 3 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

The invention claimed is:

1. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization adjuvant, and

wherein said fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of said pharmaceutical composition, and further wherein said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of said pharmaceutical composition.

2. The pharmaceutical composition of claim 1, wherein said binding cellulose derivative is hydroxypropylmethylcellulose (HPMC).

3. The pharmaceutical composition of claim 2, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

4. The pharmaceutical composition of claim 1, wherein said fenofibrate is present in an amount greater than or equal to 70% by weight, relative to the weight of said pharmaceutical composition.

5. The pharmaceutical composition of claim 1, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

6. The pharmaceutical composition of claim 1, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

7. The pharmaceutical composition of claim 2, wherein said fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. The pharmaceutical composition of claim 1, wherein said pharmaceutical composition further comprises at least one excipient.

9. The pharmaceutical composition of claim 1, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

10. The pharmaceutical composition of claim 1, wherein said composition is contained in gelatin capsules.

11. A method for preparing the pharmaceutical composition of claim 1, wherein said granules are prepared by

spraying onto neutral microgranules an aqueous suspension of micronized fenofibrate containing surfactant and solubilized binding cellulose derivative.

12. The pharmaceutical composition of claim **3**, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

13. The pharmaceutical composition of claim **1**, wherein said fenofibrate is present in an amount greater than or equal to 75% by weight, relative to the weight of said pharmaceutical composition.

14. The pharmaceutical composition of claim **1**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

15. The pharmaceutical composition of claim **1**, wherein said binding cellulose derivative represents between 5 and 12% by weight, relative to the weight of said pharmaceutical composition.

16. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

17. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of lactose, α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)], a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide, and talc.

18. The pharmaceutical composition of claim **1**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

19. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1.

20. The pharmaceutical composition according to claim **19**, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

21. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 18 cP.

22. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 3.6 cP.

23. The pharmaceutical composition of claim **19**, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

24. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

25. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

26. The pharmaceutical composition of claim **19**, wherein said pharmaceutical composition further comprises at least one excipient.

27. The pharmaceutical composition of claim **26**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

28. The pharmaceutical composition of claim **27**, wherein said diluent is lactose.

29. The pharmaceutical composition of claim **27**, wherein said antifoaming agent is α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide.

30. The pharmaceutical composition of claim **27**, wherein said lubricant is talc.

31. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

32. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

33. The pharmaceutical composition of claim **19**, wherein said composition is contained in gelatin capsules.

34. The pharmaceutical composition of claim **2**, wherein at least 95% of said fenofibrate is dissolved at 30 minutes, as measured using a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N.

* * * * *

Exhibit B


US007863331B2

(12) **United States Patent**
Criere et al.

(10) **Patent No.: US 7,863,331 B2**
(45) **Date of Patent: *Jan. 4, 2011**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF**

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(73) Assignee: **Ethypharm**, Saint Cloud (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1259 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/677,861**

(22) Filed: **Oct. 3, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 10/030,262, filed as application No. PCT/FR00/01971 on Jul. 7, 2000, now Pat. No. 7,101,574.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A61K 31/19 (2006.01)
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **514/571**; 424/465

(58) **Field of Classification Search** 514/571; 424/465

See application file for complete search history.

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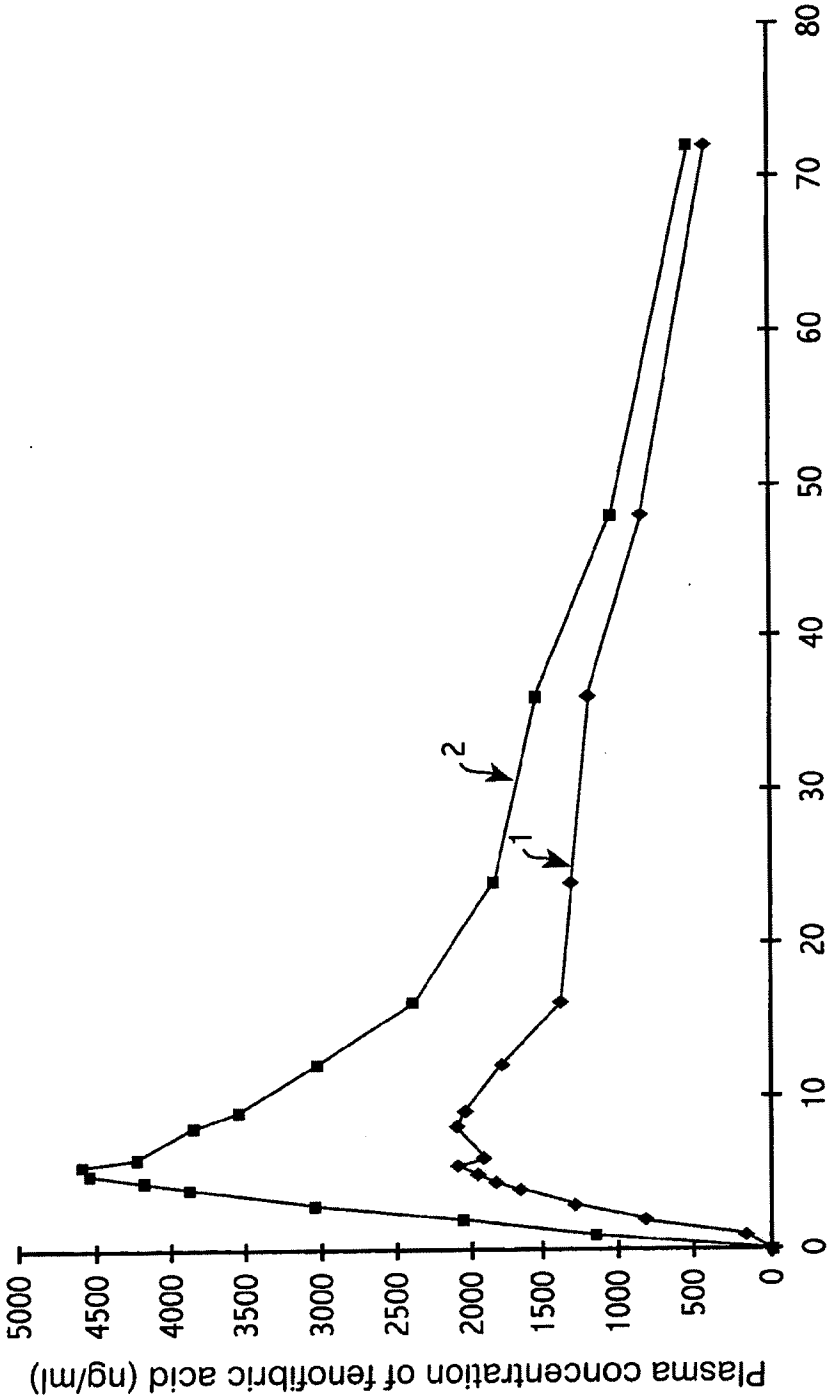
Assistant Examiner—Shirley V Gembeh
(74) *Attorney, Agent, or Firm*—Buchanan Ingersoll & Rooney PC

(57) **ABSTRACT**

Pharmaceutical compositions comprising micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, wherein said compositions contain an amount of fenofibrate greater than or equal to 60% by weight and methods of producing fenofibrate compositions.

4 Claims, 5 Drawing Sheets


Plasma concentration of fenofibric acid (ng/ml)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
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0
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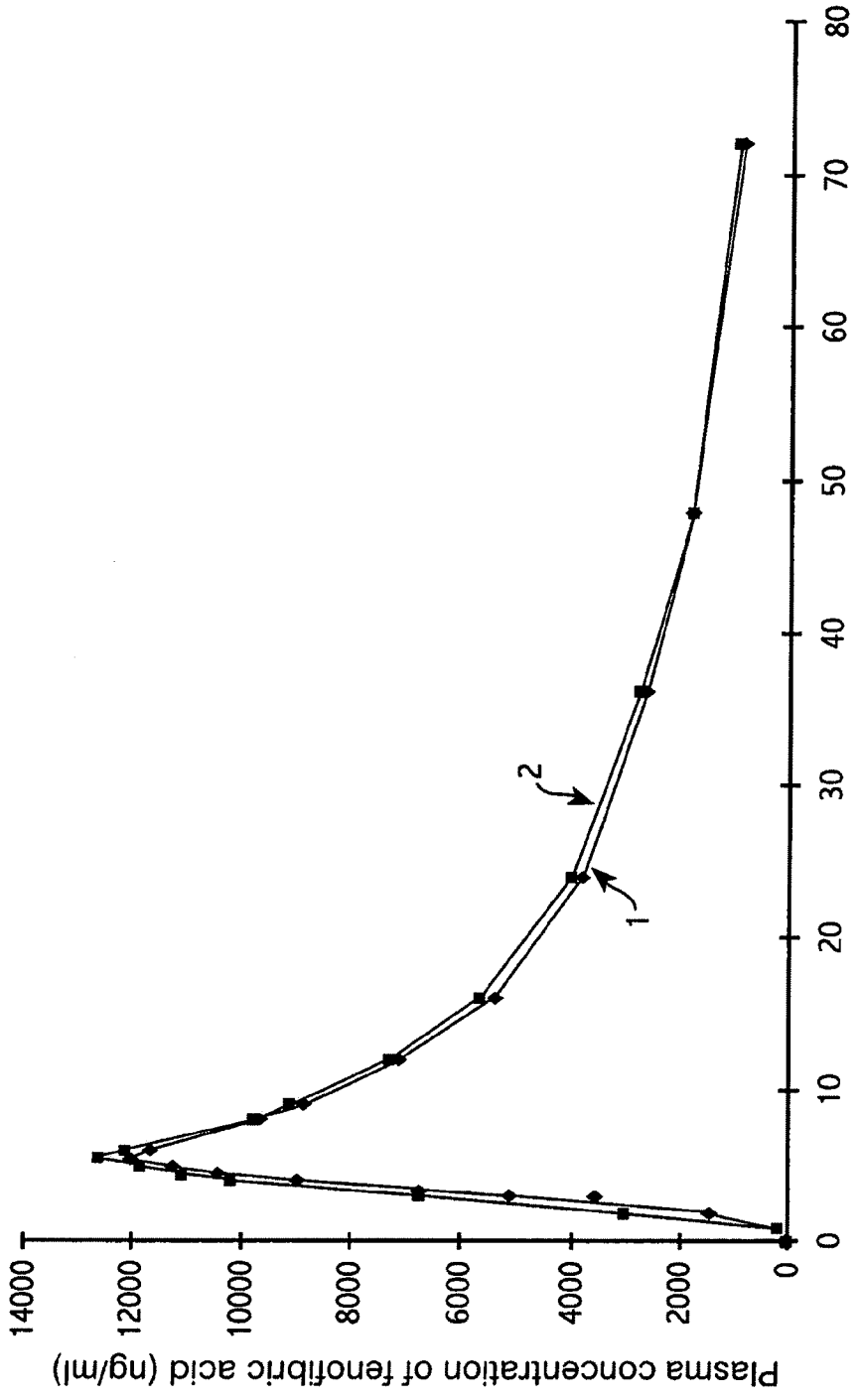
20
30
40
50
60
70
80
Time (hours)
1
2

FIG. 1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14000
12000
10000
8000
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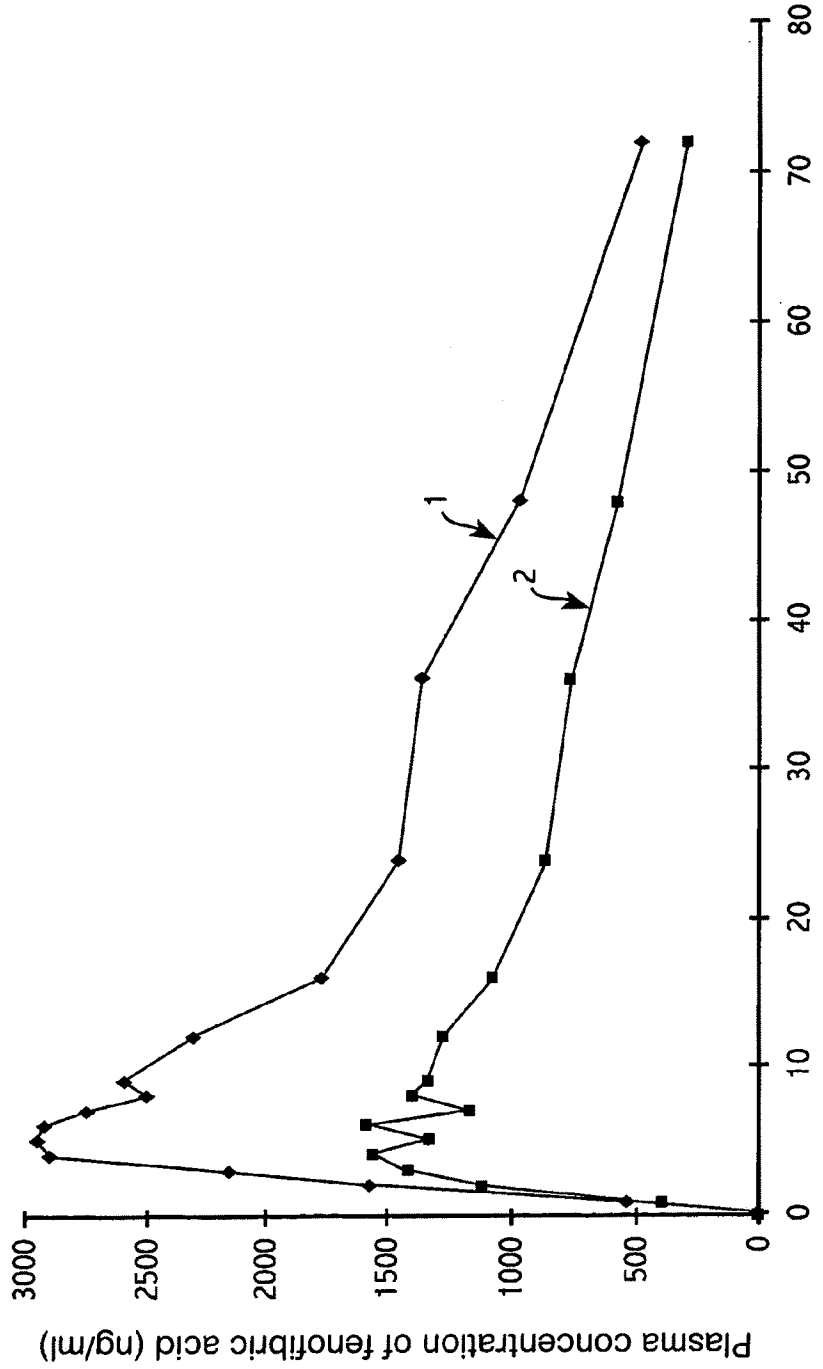
2000
0
Time (hours)
0
10
20
30
40
50
60
70
80
1
2

FIG. 2


Plasma concentration of fenofibric acid (ng/ml)
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2500
2000
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0
0
10
20
30
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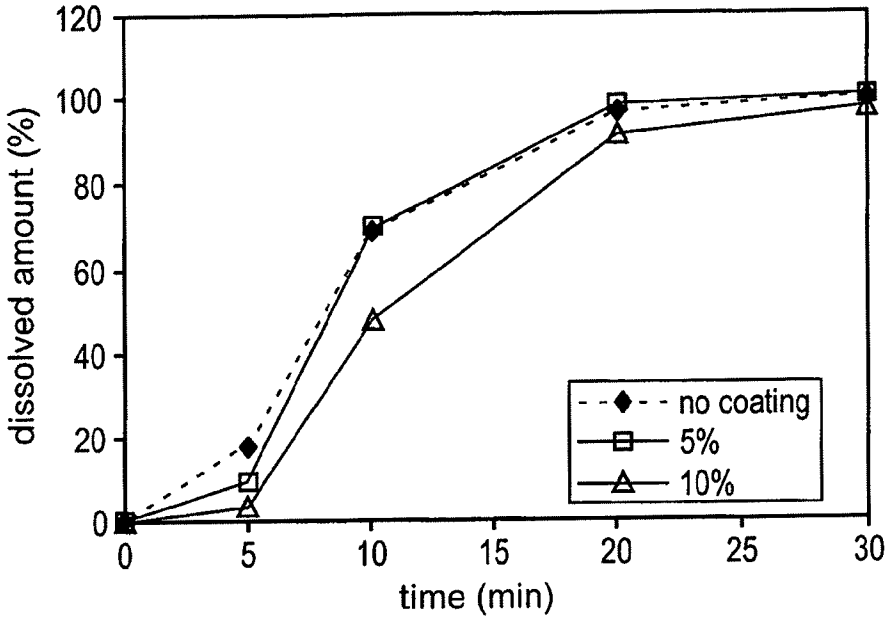
50
60
70
80
Time (hours)
1
2

FIG. 3


120
100
80
60
40
20
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dissolved amount (%)
0
5
10
15
20
25
30
time (min)
no coating
5%
10%

FIG. 4

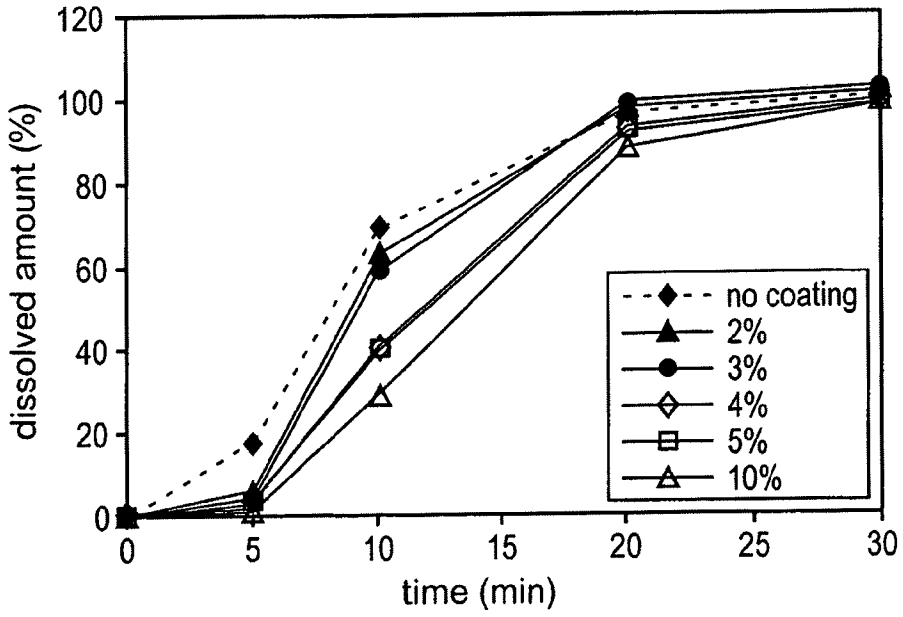
120
100
80
60
40
20
0
dissolved amount (%)
0
5
10
15
20
25
30
time (min)
no coating
2%
3%
4%
5%
10%

FIG. 5

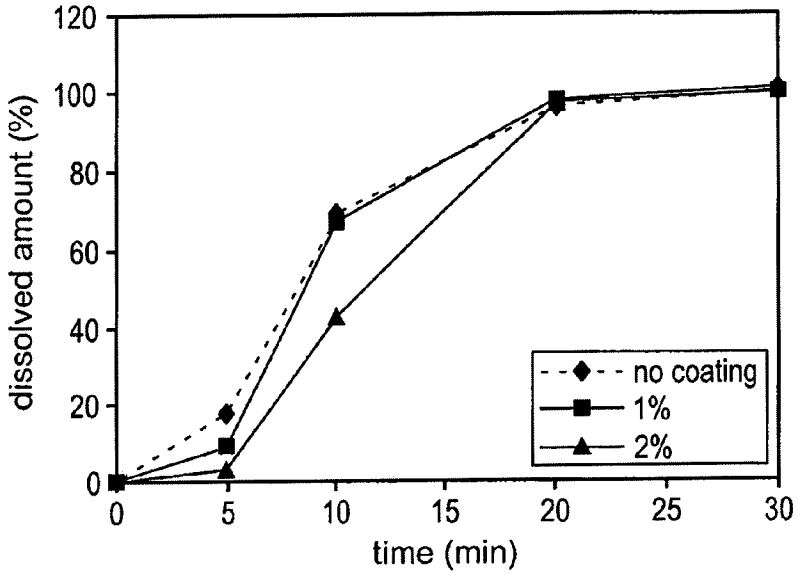
120
100
80
60
40
20
0
dissolved amount (%)
0
5
10
15
20
25
30
time (min)
no coating
1%
2%

FIG. 6

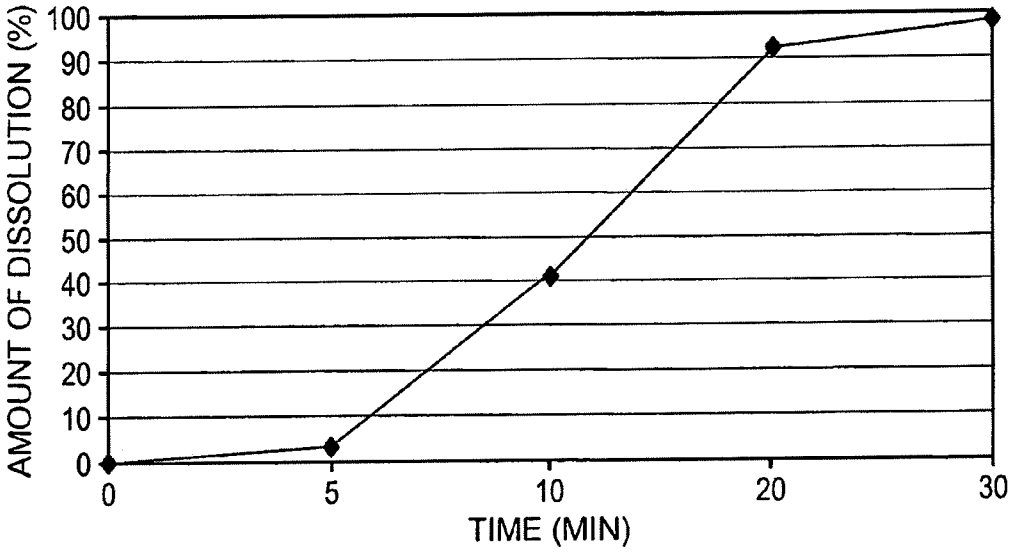
AMOUNT OF DISSOLUTION (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
20
30
TIME (MIN)

FIG. 7

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

BACKGROUND OF THE INVENTION

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited.

Due to its poor affinity for water and to its hydrophobic nature, fenofibrate is much better absorbed after ingestion of food, than in fasting conditions. This phenomenon called "food effect" is particularly important when comparing fenofibrate absorption in high fat meal conditions versus fasting conditions.

The main drawback in this food effect is that food regimen must be controlled by the patient who is treated with fenofibrate, thereby complicating the compliance of the treatment. Yet, as fenofibrate is better absorbed in high fat meal conditions, it is usually taken after a fat meal. Therefore, these conditions of treatment are not adapted to patients treated for hyperlipidemia or hypercholesterolemia who must observe a low fat regimen.

A way to limit the food effect is to increase the solubility or the rate of solubilization of fenofibrate, thereby leading to a better digestive absorption, whichever the food regimen.

DESCRIPTION OF THE RELATED ART

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline fenofibrate microparticles are less than 50 μm in size. The binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinylpyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant. It has further been discovered the pharmaceutical composition of the present invention makes it possible to obtain comparable bioavailability to prior art formulations containing a higher dosage of micronized fenofibrate.

More particularly, it has been observed that bioavailability of fenofibrate is increased when microgranules according to the present invention are prepared by mixing together in a liquid phase the fenofibrate, the surfactant and the binding cellulose derivative before spraying this liquid phase onto neutral cores.

Indeed, both cellulose derivative and surfactant are dissolved in the liquid phase in which the microparticles of micronized fenofibrate are in suspension.

Thus, when the solvent is removed from the suspension by evaporation after spraying onto neutral cores, molecules of both cellulose derivative and surfactant are adsorbed directly onto the fenofibrate microparticles. This phenomenon induces a very homogeneous repartition and creates a very close contact between fenofibrate microparticles and these molecules, which are responsible for its better solubilization in the gastro-intestinal fluids and thereby allow a better absorption of fenofibrate, also contributing to a reduction of the food effect as mentioned above.

Thus, it has been discovered that the pharmaceutical composition of the present invention has less food effect than prior art formulations when administered to patient, i.e. the inventive formulation is less dependent on the presence of food in the patient to achieve high bioavailability. For example, prior art fenofibrate formulations must be taken with food to achieve high bioavailability. The inventors have unexpectedly discovered a fenofibrate composition that achieves high bioavailability almost independent of the presence of food in a patient.

Finally, it has been discovered that the addition of an outer layer of a hydrosoluble binder results in a novel in vivo profile, with the following limits: less than 10% in 5 minutes and more than 80% in 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, that become intimately associated after the removing of the solvent used in the liquid phase.

The composition of the invention is advantageously provided as gelatin capsules containing granules. These granules may in particular be prepared by assembly on neutral cores, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

For example, the pharmaceutical composition of the present invention may include a composition in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, which surrounds the neutral core;

wherein said neutral core may include lactose, mannitol, a mixture of sucrose and starch or any other acceptable sugar, and wherein said active layer comprises the micronized fenofibrate, the surfactant and the binding cellulose derivative.

Or, for example, the pharmaceutical composition of the present invention may include an immediate release fenofibrate composition including (a) a neutral core; (b) an active layer, which surrounds the core; and (c) an outer layer; wherein the active layer comprises micronized fenofibrate, a surfactant and a binding cellulose derivative.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer. Further, the pharmaceutical composition of the present invention provides comparable bioavailability to prior art formulations at higher dosage strengths of fenofibrate. Thus, the inventive composition provides advantages over prior art formulations. For example, the inventive formulation containing only 130 mg of fenofibrate has comparable bioavailability with a prior art formulation containing 200 mg of fenofibrate under fed or fasted conditions, and with single or multiple dosing.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 (polyoxyethylene 20 sorbitan monooleate), Montane® 20 or sucrose stearate, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between about 1 and 10%, preferably between about 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between about 2 and 20%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between about 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 μm, preferably 10 μm, even more preferably less than 8 μm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance Dimethicone® (α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)]) and Simethicone® (mixture of α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)] with silicon dioxide), or lubricants, for instance talc or colloidal silicon dioxide such as Aerosil®.

The antifoaming agent may represent between about 0 and 10%, preferably between about 0.01 and 5%, even more preferably between about 0.1 and 0.7%, by weight of the composition.

The lubricant may represent between about 0 and 10%, preferably between about 0.1 and 5%, even more preferably between about 0.2 and 0.6%, by weight of the composition.

The composition of the invention may also include a outer coating or layer of a hydrosoluble binder. The hydrosoluble binder of the outer layer represents between about 1 and 15%, preferably between about 1 and 8%, even more preferably between about 2-4% by weight of the composition. The hydrosoluble binder may include hydroxypropylmethylcellulose, polyvinylpyrrolidone, or hydroxypropylcellulose or a mixture thereof. However, one of ordinary skill in the art would understand other substances that may be used as the hydrosoluble binder in the outer layer.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 3 and 15 cP, such as for example Pharmacoat 606®, or a mixture of different grades varying in viscosity. The amount of HPMC in the outer layer is inversely proportional to viscosity. It is within the skill in the art to determine the amount of hydrosoluble binder to obtain the claimed properties in the dissolution profile.

The outer layer may also include one or more excipient such as lubricants, for instance talc. The lubricant may represent between about 0 and 10%, preferably between about 1 and 5%, even more preferably between about 1-2%, by weight of the composition.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably between 130 and 200 mg and more preferably equal to 200 mg.

These granules preferably comprise:

(a) a neutral core;

(b) an active layer, which surrounds the core; and

(c) an outer layer.

The expression "outer layer" means an outer coating which is applied on the neutral core (A) coated with the active layer (B). Said coating may consist of one or several layers.

The outer layer may comprise a hydrosoluble binder.

The hydrosoluble binder of the outer layer may include hydroxypropylmethylcellulose, polyvinylpyrrolidone, or hydroxypropylcellulose. However, one of ordinary skill in the art would understand other substances that may be used as the binding cellulose derivative in the outer layer.

In the outer layer, hydroxypropylmethylcellulose is preferably chosen among Hydroxypropylmethylcellulose having an apparent viscosity of 3 cP, such as Pharmacoat 603®, or 6 cP, such as Pharmacoat 606®, or 15 cP such as Pharmacoat 615®.

The outer layer may further comprise talc. In that case, the HPMC/talc mass ratio is preferably comprised between 1/1 and 5/1.

The present invention also relates to a pharmaceutical composition of fenofibrate that can be administered to provide substantial reduction of an effect of food on the uptake of the fenofibrate, i.e. substantial reduction of the food effect.

Such a pharmaceutical composition presents the advantage of being almost independent of the food conditions. Such a composition substantially reduces or eliminates the difference of bioavailability observed in function of the nature of the meal and between fed and fasted conditions.

Indeed, food can change the bioavailability of a drug, which can have clinically significant consequences. Food can alter bioavailability by various means, including: delaying gastric emptying, stimulating bile flow, changing gastrointestinal (GI) pH, increasing splanchnic blood flow, changing luminal metabolism of a drug substance, and physically or chemically interacting with a dosage form or a drug substance. Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested, such as provided in prior art fenofibrate formulations. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. Notably, fenofibrate is prescribed for cholesterol management to patients who cannot eat high fat foods. Thus, there is a need for a fenofibrate composition that need not be administered with high fat foods. The present invention, unlike prior art fenofibrate formulation, achieves high bioavailability irrespective of the presence of food.

Accordingly, a method of reducing food effect is provided when treating hyperlipidemias, hypercholesterolemias and hypertriglyceridemias in a patient, including the steps of administering to the patient an effective amount of the instant invention. Further, the bioavailability of the composition is equivalent whether the patient is fed a high fat meal, a therapeutic lifestyle change diet, or when the patient is fasted.

In addition, the invention provides a composition comprising fenofibrate having a novel in vivo dissolution profile of less than 10% in 5 minutes and more than 80% in 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

The composition according to the present invention, advantageously has a dissolution profile less than 5% at 5 minutes and more than 90% at 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopeia in a dissolution medium constituted by water with 0.25M sodium lauryl sulfate.

The present invention also relates to a method for preparing the granules, the composition of which is described above. This method uses no organic solvent.

The granules are prepared by assembly on neutral cores.

The neutral cores have a particle size of between 200 and 1000 microns, preferably between 400 and 600 microns. The neutral cores may represent between about 1 and 50%, preferably between about 10 and 20%, even more preferably between about 14-18%, by weight of the composition.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly on neutral cores is carried out by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension, and then optionally, by spraying an aqueous solution containing the the hydrosoluble binder.

The invention is illustrated in a non limiting way by the following examples

BRIEF DESCRIPTION OF THE DRAWING FIGURES

FIG. **1** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals. (Curve 1: Lipanthyl® 200M; Curve 2: composition according to the present invention).

FIG. **2** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals in fed condition. (Curve 1: Lipanthyl® 200M; Curve 2: composition according to the present invention).

FIG. **3** represents the in vivo release profile of the formulation of comparative example 2 and of a formulation of the prior art in individuals in fed condition.

FIG. **4** represents the in vitro dissolution profile as a function of the amount of the (HPMC 603/Talc) suspension applied on the microgranules.

FIG. **5** represents the in vitro dissolution profile as a function of the amount of the (HPMC 606/Talc) suspension applied on the microgranules.

FIG. **6** represents the in vitro dissolution profile as a function of the amount of the (HPMC 615/Talc) suspension applied on the microgranules.

FIG. **7** represents the in vitro dissolution profile as a function of the amount of the (HPMC 606/Talc) 4% suspension applied on the microgranules.

EXAMPLES

Although the present invention has been described in detail with reference to examples above, it is understood that various modifications can be made without departing from the spirit of the invention, and would be readily known to the skilled artisan. Additionally, the invention is not to be construed to be limited by the following examples.

Example 1

Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension of micronized fenofibrate onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral cores	21

-continued

Formula	Amount (percentage by mass)
HPMC (Pharmacoat 603 ®)	11.2
Polysorbate ® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at. 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, 15 Lipanthyl 200 M, are given in the following table.

	Time (min)	
	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9±0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC. The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral cores	20.1
HPMC (Pharmacoat 603 ®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral cores is between 400 and 600 μm.

1C) Gelatin Capsules of Microgranules (Y FEN 001)

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral cores	17.2
Pharmacoat 603 ® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

	Time (min)	
	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40° C./75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

	Conservation time			
	0	1 month	3 months	6 months
Content (mg/gelatin Capsule)	208.6	192.6	190.8	211.7

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the example 1C granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. 1.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{o-t} (μg · h/ml)	76	119
AUC_{inf} (μg · h/ml)	96	137
C_{max} (μg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the C_{max},

Elim ½: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **1** by curves 1 and 2, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic Study Carried Out in Individuals in Fed Condition

The in vivo release profile of the gelatin capsules containing the example 1C granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **2**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{o-t} (µg · h/ml)	244	257
AUC_{inf} (µg · h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **2** by curves 1 and 2, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals in fed condition.

Comparison of the Pharmacokinetic in Individuals Under Fed Condition Versus the Pharmacokinetic in Fasting Individuals

Under fasted conditions it was unexpectedly found that the formulation of the invention provided a statically significant increased relative bioavailability of approximately 1.4 times that of the Lipanthyl® as evidenced by a 100% higher mean maximum concentration (C_{max}) of the drug and approximately 62% higher mean AUC's. This significant difference between the two formulations disappeared under fed condition.

When the bioavailability of the Lipanthyl® under fed versus fasted conditions was compared, the C_{max} significantly increased (418%) and the mean AUC's significantly increased by (152%).

In contrast, when the bioavailability of the formulation of this invention under fed versus fasted conditions was compared, the C_{max} significantly increased by only 170% and the mean AUC'S were increased only by 76%.

The formulation according to the invention provides a pharmacokinetic profile in which the effect of ingestion of food on the uptake of the drug is substantially reduced over that observed with Lipanthyl®.

Comparative Example 2

Batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

Theoretical formula

Products	Theoretical amount %
Micronized fenofibrate	75.08
Montanox 80 ®	4.72
Avicel PH 101 ®	5.02
PVP K 30 ®	4.12
Explotab ®	11.06

In vitro dissolution profile

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in 10 the following table.

	Time (min)	
	15	30
Example 2 (% dissolved)	24	40
Lipanthyl 200 M (% dissolved)	47.3	64.7

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **3**.

Pharmacokinetic Parameters	Lipanthyl 200 M	Example 2
AUC_{o-t} (µg · h/ml)	92	47
AUC_{inf} (µg · h/ml)	104	53
C_{max} (µg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 2 are represented on FIG. **3** by curves 1 and 2, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 2 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not

make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

Example 3

Microgranules Coated with an Outer Layer

Microgranules were prepared by spraying an aqueous suspension onto neutral cores.

The composition of the suspension is given in the following table:

Suspension	Amount (percentage by mass)
Purified water	78.09
35% dimethicone emulsion	0.19
30% simethicone emulsion	0.03
HydroxyPropylMethylCellulose (HPMC) 2910 (Pharmacoat ® 603)	3.31
Sodium lauryl sulphate	0.89
Micronized fenofibrate	17.49
Total	100.00

The composition of the obtained microgranule is given in the following table:

Formula of microgranules	Amount (kg)
Micronized fenofibrate	372.00
Sugar spheres	96.00
HydroxyPropylMethylCellulose (HPMC) 2910 (Pharmacoat ® 603)	70.32
Sodium lauryl sulphate	18.96
35% dimethicone emulsion	4.12
30% simethicone emulsion	0.67
Talc	2.72
Purified water	1660.80

Different additional outer layers composed of a suspension of HPMC and talc (2:1, w:w) were applied on the obtained microgranules. They differ from each other:

- by the type of HPMC used: Pharmacoat® 603, 606 or 615. The major difference between these HPMC is their viscosity which increases in the order HPMC 603<HPMC 606<HPMC 615.
- by the amount of the (HPMC/Talc) suspension applied on the microgranules: 1, 2, 3, 4, 5 or 10%, expressed as dry HPMC/talc relative to the total microgranule.

Dissolution tests were performed with hand-filled gelatine capsules. The mass of microgranules introduced in the capsule was calculated according to the theoretical content of fenofibrate in the formula.

The equipment was composed of:

- a dissolutest (for example: SOTAX AT7 type),
- a pump which allows direct sample analysis,
- a UV spectrophotometer (for example: Lambda 12 from Perkin Elmer).

The dissolution method used was a rotating blade method at 75 rpm according to the European Pharmacopoeia.

The dissolution medium was composed of water with 0.025 M sodium lauryl sulfate. The temperature was set at 37.0° C.±0.5° C.

Dissolution profile as a function of the amount of the (HPMC/Talc) suspension applied on the microgranules

The effect exerted on the dissolution profile by the amount of the HPMC/Talc suspension applied on the microgranules was studied. The results are summarized on FIGS. **4** to **6** for HPMC 603, 606 and 615 respectively.

The coating leads to the apparition of a delay after 5 min dissolution.

Example 4

Microgranules Coated with an Outer Layer Applied by Spraying a (HPMC 606/Talc) 4% Suspension

Microgranules are obtained by spraying an aqueous suspension of micronized fenofibrate prepared as described in example 3 onto neutral cores, followed by an outer layer of HPMC and talc, the composition of the microgranules is given in the following table:

FORMULA	PERCENTAGE BY MASS
Neutral cores	16.44
Micronized fenofibrate	63.69
Hydroxypropylmethyl cellulose 3.0 Viscosity cP	12.04
Sodium lauryl sulfate	3.25
Dimethicone	0.25
Simethicone	0.03
Talc	0.63
Outer layer	
Hydroxypropylmethyl cellulose 6.0 Viscosity cP	2.57
Talc	1.1

Example 5

Dissolution Profile

A dissolution profile for a fenofibrate composition prepared according to example 4 was carried out by rotating blade method at 75 rpm, according to the European Pharmacopoeia. The dissolution medium was composed of water with 0.025 M sodium lauryl sulfate. The temperature was set at 37° C.±0.5° C.

The vessel was filled with 1000 mL sodium lauryl sulfate 0.025 M. One hand-filled capsules were added to the vessel. The test sample was taken at time intervals of 5 minutes (during 1 hour) and analyzed at a wavelength of 290 nm, through 2 mm quartz cells, against a blank constituted of 0.025 M sodium lauryl sulfate. The results obtained are shown graphically in FIG. 7, on which the percentage of dissolution is shown and in the following table.

Time (min)	Amount of dissolution (%)
5	3 ± 1
10	41 ± 7
20	92 ± 4
30	98 ± 1

These results clearly show that the composition according to the invention has a dissolution profile which is less than 10% in five minutes and more than 80% in 20 minutes.

Example 6

A comparison of the relative bioavailability of 130 mg fenofibrate composition prepared according to example 4 and Tricor® 200 mg under fasted conditions and following consumption of a standard high fat FDA test meal in healthy adult subjects.

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 32 healthy volunteers in a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed. Subjects randomized to treatment A received a single oral dose of 130 mg fenofibrate prepared according to example 4 taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment B received a single oral dose of the same formulation taken with 240 mL of tap water following a standardized high-fat meal. Subjects randomized to Treatment C received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment D received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a standardized high-fat meal.

In these examples, "fasted" is based on a 10-hour absence of food, however, a skilled artisan would know other methods of preparing fasted conditions. For example, "fasted" may be understood as 10 hour or more absence of food.

The standardized high-fat meal contains approximately 50 percent of total caloric content of the meal from fat or a calorie content of 800-1000 calories of which 50 percent is from fat. An example of the standardized high-fat meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes (fired with butter) and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The results obtained are given in Tables 1 and 2 below:

TABLE 1

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Standard High-Fat FDA Test Meal) Conditions

Parameter	Treatment A Invention 130 mg (Fasted)	Treatment B Invention 130 mg (Fed)	Treatment C Tricor ® 200 mg (Fasted)	Treatment D Tricor ® 200 mg (Fed)
AUC_{0-t} (ng · h/mL)	114853	145562	109224	224330
AUC_{0-inf} (ng · h/mL)	116134	146843	111235	226004
C_{max} (ng/mL)	4375	9118	3413	12829
T_{max} (h)	4.84	4.89	9.61	5.65
$t_{1/2}$ (h)	19.7	18.3	21.0	19.0

TABLE 2

Fed vs Fasted Ratios for Individual Formulations

Parameter	B: Invention 130 mg (Fed) vs A: Invention 130 mg (Fasted)	D: Tricor ® 200 mg (Fed) vs C: Tricor ® 200 mg (Fasted)
AUC_{0-t}	124.8	221.1
AUC_{0-inf}	124.6	218.8
C_{max}	210.2	434.2

Table 1 shows that the extent of absorption (AUC) of fenofibric acid following administration of 130 mg fenofibrate of the invention is comparable to that of the Tricor® 200 mg capsule under fasted conditions.

In addition, table 2 shows that the maximum plasma concentration (C_{max}) for the invention is lower than Tricor®, indicating that food effected the rate of bioavailability for the Tricor® formulation. Specifically, the food effect observed for the invention is approximately 2-fold lower than that observed for the Tricor® 200 mg capsule. This suggests that the rate of bioavailability for the invention is almost independent of the presence of food. In contrast, the rate of bioavailability for Tricor® significantly increased with food.

Example 7

A comparison of the relative bioavailability of 130 mg fenofibrate composition prepared according to in example 4 versus Tricor® 200 mg capsules at steady state in healthy adult subjects on a Therapeutic Lifestyle Change Diet ("TLC").

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 28 healthy volunteers in a randomized, multiple-dose, open-label (laboratory-blinded), 2-way crossover study to determine and compare the bioavailability of the formulation prepared according to example 4 of the invention relative to Tricor® 200 mg oral capsules immediately following consumption of a TLC diet meal. Subjects randomized to Treatment A received a single oral dose of one 130 mg capsule of the invention taken with 240 mL of room temperature tap water daily for 7 days. Subjects randomized to Treatment B received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of room temperature tap water daily for 7 days.

The TLC Diet stresses reductions in saturated fat and cholesterol intake. The TLC diet contains approximately 25-30 percent fat per meal. An example of a TLC meals is 1 cup of bran cereal, 1 cup of fat free milk, 8 ounces of orange juice, 1 small banana, 1 slice whole wheat toast, 1 teaspoon of margarine, and coffee, black or with fat free milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The results obtained are given in Table 3 below:

TABLE 3

Pharmacokinetic Parameters for Fenofibric Acid Following Multiple Dosing in Healthy Subjects on a TLC Diet

Parameter	Treatment A Invention 130 mg (Fed)	Treatment B Tricor ® 200 mg (Fed)
$AUC_{\tau, ss}$ (ng · h/mL)	182889	204988
$C_{max, ss}$ (ng/mL)	12664	13810
$T_{max, ss}$ (h)	4.896	5.343
$C_{av, ss}$ (ng/mL)	7620	8541
$C_{min, ss}$ (ng/mL)	4859	5878

The results on table 3 show that the bioavailability of the capsules of the invention and the Tricor® 200 mg capsules are comparable after multiple dosing, immediately following consumption of a TLC diet meal.

Example 8

A Comparison of the Relative Bioavailability of 130 mg fenofibrate composition prepared according to example 4 and Tricor® 200 mg Under Fasted Conditions and Following Consumption of a Therapeutic Lifestyle Change Meal in Healthy Adult Subjects.

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 32 healthy volunteers in a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability of 130 mg of the invention prepared according example 4 to Tricor® 200 mg oral capsules under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed. Subjects randomized to Treatment A received a single oral dose of 130 mg fenofibrate prepared according to example 4 taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment B received a single oral dose of 130 mg fenofibrate prepared according to example 4 formulation taken with 240 mL of room temperature tap water following a TLC meal. Subjects randomized to Treatment C received a single oral dose of one Tricor® 200 mg capsule taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment D received a single oral dose of one Tricor® 200 mg capsule taken with 240 mL of tap water following a TLC diet meal.

The results obtained are given in Tables 4 and 5 below:

TABLE 4

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Therapeutic Lifestyle Change Meal) Conditions

Parameter	Treatment A: Invention 130 mg (Fasted)	Treatment B: Invention 130 mg (Fed)	Treatment C: Tricor ® 200 mg (Fasted)	Treatment D: Tricor ® 200 mg (Fed)
AUC_{0-t} (ng · h/mL)	126031	130400	123769	159932
AUC_{0-inf} (ng · h/mL)	128020	132387	129798	162332

TABLE 4-continued

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Therapeutic Lifestyle Change Meal) Conditions

Parameter	Treatment A: Invention 130 mg (Fasted)	Treatment B: Invention 130 mg (Fed)	Treatment C: Tricor ® 200 mg (Fasted)	Treatment D: Tricor ® 200 mg (Fed)
C_{max} (ng/mL)	4403	7565	2734	7554
T_{max} (h)	4.73	4.21	8.37	4.58

TABLE 5

Fed vs. Fasted Ratios for Individual Formulations

Parameter	B: Invention 130 mg (Fed) vs A: Invention 130 mg (Fasted)	D: Tricor ® 200 mg (Fed) vs C: Tricor ® 200 mg (Fasted)
AUC_{0-t}	104.0	131.4
AUC_{0-inf}	103.9	127.9
C_{max}	175.1	279.7

The results on Table 4 show that following the consumption of a TLC meal, the maximum plasma concentration (C_{max}) of fenofibric acid and the extent of absorption (AUC) of the invention is comparable to Tricor®. Similarly, under fasted conditions, the extent of absorption (AUC) of the invention is comparable to Tricor®. But, the maximum plasma concentration (C_{max}) of fenofibric acid is greater for the invention than for the Tricor® formulation indicating that the invention is more easily absorbed.

Also, the results on Table 5 show that the consumption of a TLC meal effected the maximum plasma concentration (C_{max}) for both the invention and Tricor®. But the food effect is more than 2-fold lower for the invention as compared to Tricor®. This indicates that the rate of bioavailability for the invention is almost independent of the presence of food. In contrast, the rate of bioavailability for Tricor® significantly increased with food.

What is claimed is:

1. A method of reducing food effect when treating hypertriglyceridemias and/or hypercholesterolemias and/or hyperlipidemias in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising micronized fenofibrate, a surfactant and hydroxypropylmethylcellulose, wherein said composition is in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, surrounding the neutral core;

wherein said neutral core comprises a sugar or a sugar mixed with starch; said active layer comprises the micronized fenofibrate, the surfactant, and the binding cellulose derivative; and wherein the mass ratio of said fenofibrate to said hydroxypropylmethylcellulose is between 5/1 and 15/1, and said hydroxypropylmethylcellulose represents between 5 and 12% by weight of the composition.

2. The method of claim 1, wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

3. The method of claim 1, wherein said patient is fed at least 800-1000 calories, 50% of which are from fat, and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

4. The method of claim 1, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

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